Experimental Use of GnRH Antagonists as Second-Line Hormonal Therapy

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The hypothesis that follicle-stimulating hormone (FSH) signaling contributes to the progression of androgen-independent prostate cancer (AIPC) is supported by preclinical evidence. Therefore, abarelix, a gonadotropin-releasing hormone antagonist that suppresses circulating FSH more effectively than standard hormone therapies, would be expected to reduce FSH without altering testosterone, thereby testing the hypothesis that circulating FSH supports the progression of AIPC. The authors tested abarelix on 2 groups of men with early AIPC: 1 group had undergone luteinizing hormone-releasing hormone agonist therapy and the other had undergone orchiectomy. Although there was no confirmed response in either group, the investigators found the time to progression, fraction of patients progression-free at the end of therapy, and fraction of patients with confirmed prostate-specific antigen reductions less than 50% were all higher in the orchiectomy-treated patients. This hypothesis-generating observation has led to a phase I trial to determine whether an escalation in the dosage of abarelix is safe and will produce more complete suppression of FSH.
[Rev Urol. *2004;6(suppl 7):S33-S38*]

Key words: Prostate cancer • Abarelix • Follicle-stimulating hormone

Preclinical evidence supports the hypothesis that follicle-stimulating hormone (FSH) signaling contributes to the progression of androgen-independent prostate cancer (AIPC). The gonadotropin-releasing hormone (GnRH) antagonist abarelix suppresses circulating FSH more effectively than do standard hormonal therapies (luteinizing hormone-releasing hormone [LHRH] agonists and

orchiectomy). When tested in patients who are progressing after orchiectomy or LHRH agonist therapy, abarelix would be expected to reduce serum FSH without altering testosterone and could therefore be used to test the hypothesis that circulating FSH supports the progression of AIPC. We tested abarelix 100 mg intramuscularly on days 1, 15, and 29, then every 28 days for up to 24 weeks in 36 patients with early AIPC who were progressing either after LHRH agonist therapy (n = 20) or orchiectomy (n = 16). Treatment was well tolerated and produced significant reduction in circulating FSH in both populations. In the orchiectomy group, which started therapy with FSH levels nearly 10-fold higher than the LHRH agonist group, FSH was reduced by nearly 90%, but suppression was not complete, perhaps because of the chronic elevation of FSH in those patients. There were no confirmed responses to abarelix in either group; however, time to progression, fraction of patients progression-free at the end of the planned 24-week course of therapy, and fraction of patients with confirmed prostate-specific antigen (PSA) reductions less than 50% were all higher in the orchiectomy-treated patients. The observation, which must be viewed as hypothesis generating, led to the development of a phase I trial of more frequently dosed abarelix in AIPC. In addition to safety, this trial seeks to determine whether escalating the dose of abarelix in this setting will produce more complete suppression of FSH. If successful, this trial will lead to additional studies aimed at testing the efficacy of this approach in AIPC patients.

Preclinical Rationale

Follicle-stimulating hormone may be an interesting new therapeutic target in prostate cancer. Preclinical evidence supports the hypothesis that FSH signaling contributes to progression of AIPC. FSH receptors (FSH-Rs) are expressed in both prostate cancer cell lines and human prostate cancer specimens.[1,2] In human specimens, FSH-R expression is increased in prostate cancer specimens when compared with normal prostate tissue.[2]

Follicle-stimulating hormone signaling through its receptor may be an interesting new therapeutic target in prostate cancer. Preclinical evidence supports the hypothesis that FSH signaling contributes to progression of AIPC.

Signaling through the FSH-R appears to be a mitogenic (stimulatory) signal in preclinical models of prostate cancer. In androgen-independent PC-3 cells, FSH suppresses apoptosis and stimulates proliferation in vitro.[2] Cetrorelix, a GnRH antagonist, produced significant antitumor activity in a nude mouse, androgen-independent DU-145 xenograft model.[3,4] In addition to the pituitary, FSH is produced by both benign and malignant epithelial cells from the prostate; thus in prostate cancer, FSH could signal via endocrine, paracrine, or autocrine mechanisms.[1,2,5,6]

Clinical Rationale

Standard initial hormonal therapy for prostate cancer, via LHRH agonist or orchiectomy, does not completely suppress FSH.[7-9] LHRH agonists reduce but do not completely suppress FSH, whereas orchiectomy results in elevated FSH concentrations.[10-12] Estrogens have long been known to have activity in the initial management of prostate cancer and were recently recognized to have modest activity in AIPC.[13] Estrogens suppress circulating FSH. Although the activity of estrogens in AIPC could be explained by their effect on FSH, estrogens also alter testosterone, free testosterone, estradiol, dehydroepiandrosterone sulfate, sex hormone–binding globulin, and cortisol.[14,15] Further, estrogens may directly affect tumor cells through estrogen receptors. High dose estrogens are known to be cytotoxic. Because it is difficult to separate the effect of estrogens on FSH from all their other effects, it is impossible to determine whether changes in serum FSH explain the activity of estrogens in AIPC.

Unlike LHRH agonists, GnRH antagonists substantially reduce circulating FSH when used in the initial management of advanced prostate cancer.[16] Applied in the setting of AIPC, a GnRH antagonist would be expected to reduce circulating FSH without affecting already suppressed testosterone. Therefore, testing a GnRH antagonist as second-line hormonal therapy for prostate cancer affords a window through which we can begin to test the hypothesis that circulating FSH is important in the progression of AIPC.

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Phase II Studies of Abarelix in AIPC

In an effort to test the hypothesis that FSH plays a role in the progression of AIPC, we tested abarelix in 2

parallel phase II studies in early AIPC: one in patients progressing on LHRH agonist therapy and the other in patients who were progressing after orchiectomy.

Eligibility

With the exception of the different primary hormonal therapies, eligibility criteria for the 2 studies were the same and have been previously reported.[17,18] Briefly, eligible patients had histologically confirmed prostate cancer progressing despite orchiectomy or LHRH agonist therapy. Progression was defined as a 50% rise in the PSA level confirmed by 2 measurements at least 2 weeks apart, the appearance of new metastatic lesions, or progression of known metastatic disease. When used, androgen receptor antagonists were discontinued and progression was confirmed after withdrawal of these agents (6 weeks for bicalutamide, 4 weeks for flutamide or nilutamide). In addition, eligible patients met the following criteria: Eastern Cooperative Oncology Group performance status 2, age 18 years, serum testosterone 50 ng/dL, PSA 5 ng/mL, and adequate renal, hepatic, and bone marrow function.

Prior treatment for prostate cancer with chemotherapy, radiopharmaceuticals, diethylstilbesterol or another estrogen, PC-SPES, ketoconazole, or other second-line hormonal therapy (except antiandrogens) was not allowed. Patients were also excluded for allergy to an LHRH agonist or GnRH antagonist, major surgery within 4 weeks, ≥ grade 3 peripheral neuropathy, serious medical illnesses, New York Heart Association class III or IV congestive heart failure, unstable angina, myocardial infarction within 6 months, acute deep venous thrombosis, acute pulmonary embolism, or active second malignancy other than nonmelanoma skin cancer (patients in remission who had a > 30% risk for relapse were considered to have an active malignancy).

Table 1
Baseline Characteristics and Outcome of Patients Treated With LHRH Agonist or Orchiectomy Prior to Abarelix Therapy

Characteristic	LHRH	Orchiectomy	*P* Value*
Patients, n	20	16	
Age, y			
Median (range)	74 (53-92)	78 (57-86)	.13
ECOG performance status			
0	7	9	.33
1	9	6	
2	4	1	
PSA, ng/mL			
Median (range)	27 (6-201)	20 (5-445)	.42
Alkaline phosphatase, U/L			
Median (range)	87 (43-853)	75 (37-114)	.07
FSH, IU/L			
Median (range)	4 (2.7-15)	44 (17-80)	< .0001
>10, number of patients	2	16	
Site of metastases			.36†
Bone only	12	5	
Lymph nodes only	1	1	
Liver only	0	1	
Bone and lymph nodes	0	1	
None	7	8	
Any confirmed PSA reduction	1 of 20 (5%)	5 of 16 (31%)	.04
Progression-free after 6 mo	2 of 20 (10%)	6 of 16 (38%)	.049

*The Mann-Whitney U test was used for comparison of continuous variables, and the chi-square test was used for comparison of categorical variables.
†Any metastases versus no metastases.
ECOG, Eastern Cooperative Oncology Group; FSH, follicle-stimulating hormone; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.

Treatment and Assessments

Abarelix depot 100 mg was given on days 1, 15, and 29, then every 28 days for 24 weeks by intramuscular injection. Any evidence of progression led to discontinuation of study treatment. If a patient completed 24 weeks of therapy without progression, that patient was followed until progression or censored when another form of therapy was initiated. Patients were monitored at baseline and every 4 weeks with adverse event assessment, complete blood count, chemistries, PSA, and FSH. Physician visits with physical examination occurred every 12 weeks, and serum testosterone was measured after 4 and 8 weeks of therapy. When present, measurable disease was assessed every 8 weeks. In both studies, PSA response was defined as

Table 2
Number of Patients Experiencing Each Adverse Event (N = 36)

Adverse Event	Grade 1	Grade 2	≥ Grade 3
Hematologic			
Anemia	4	2	0
Leukopenia	1	0	0
Neutropenia	1	0	0
Thrombocytosis	1	0	0
Nonhematologic			
Allergic reaction/hypersensitivity	0	1	1
Fatigue	2	2	0
Anorexia	1	1	0
Dehydration	0	1	0
Weakness	1	1	0
Weight loss	0	1	0
Pain	4	0	0
Hot flashes	6	0	0
Bruising or erythema at injection site	3	0	0
Gynecomastia	2	0	0
Constipation	1	0	0
Sensory neuropathy	1	0	0
Dermatitis	1	0	0
Tinnitus	1	0	0
Nausea	1	0	0
Vomiting	1	0	0
Epistaxis	1	0	0
Laboratory			
Hyperphosphatemia	3	1	0
Hyperglycemia	5	0	0
Hypercalcemia	3	0	0
Hypophosphatemia	3	0	0
Creatinine elevation	2	0	0
Hyperchloremia	2	0	0
Alkaline phosphatase elevation	1	0	0
AST elevation	1	0	0
Bilirubin elevation	2	0	0
Hyperkalemia	2	0	0
Hypoalbuminemia	1	0	0

AST, aspartate transaminase.

by Bubley and colleagues[19] (50% reduction in PSA confirmed 4 weeks apart). Response Evaluation Criteria in Solid Tumors (RECIST) were used to assess measurable disease.[20]

Results

Patients. Twenty men who progressed on an LHRH agonist and 16 men who progressed after an orchiectomy were enrolled. Patient characteristics are summarized in Table 1. The only statistically significant difference between the 2 groups was baseline FSH, which was substantially higher in orchiectomy patients. Median duration of treatment in both groups was 16 weeks (orchiectomy range 5-28 weeks, n = 16; LHRH agonist range 6-24 weeks, n = 20).

Toxicity. Treatment was generally very well tolerated. No deaths occurred on either study. One patient died 15 days after discontinuing treatment for unconfirmed progression. Two allergic reactions were observed, 1 grade 3 from initial treatment and 1 grade 2 after 8 weeks on treatment, both resulting in discontinuation of the study drug. All toxicities deemed at least possibly related to treatment are reported in Table 2.

Efficacy: LHRH agonist group. No patients met criteria for a PSA response. One 94% PSA reduction was observed; however, this patient experienced increased skeletal pain and increased lesion intensity on bone scan while the PSA was reduced, so the patient was not classified as a PSA response. Two patients remained stable without PSA or other evidence of disease progression at the end of 6 cycles of therapy. The median time to progression was 8 weeks (95% CI, 5.7–10.3 weeks).

Efficacy: orchiectomy group. No patients met criteria for a PSA response, but lesser PSA reductions, ranging from 9.3% to 31.8%, were observed in 5 patients (31%; 95% CI, 11%-58%). Six patients had stable disease without any signs of progression at the end of 6 cycles of therapy. The median time to progression was 12 weeks (95% CI, 6–18 weeks). In the 3 patients with measurable disease at study enrollment, no measurable disease responses were seen: 2 had stable disease and 1 discontinued treatment before follow-up scans were completed.

Overall, any confirmed PSA reduction was more common in patients who had a prior orchiectomy than in LHRH agonist–treated patients (31% vs 5%, P = .04), more orchiectomy patients were progression-free at the end of 24 weeks (38% vs 10%,

P = .049), and time to progression was longer in orchiectomy-treated patients when compared with LHRH agonist–treated patients (Figure 1, log rank P = .025). Because none of these endpoints is validated and because undetected differences between the 2 study groups could also explain such observations, these findings must be considered hypothesis-generating only. Considering that serum FSH was substantially (approximately 10-fold) higher in orchiectomy patients, it was interesting that these patients had more disease stabilization on therapy than did LHRH agonist–treated patients.

Effects on FSH and testosterone. Changes in serum FSH in response to abarelix therapy were seen in both groups, but were much more striking in the orchiectomy group, which started out with substantially higher FSH concentrations. As shown in Figure 2, FSH was reduced by approximately 50% in LHRH agonist–treated patients and approximately 90% from a much higher baseline in the orchiectomy patients. In both groups, FSH suppression was maintained for the 20 weeks of monitoring. Notably, despite a nearly 90% reduction, FSH was not completely suppressed in the orchiectomy group, perhaps because it had been chronically elevated.

All patients, regardless of prior hormonal therapy, maintained anorchid testosterone concentrations on abarelix therapy.

Conclusions from the Initial Trials of Abarelix in AIPC

Neither of the 2 trials of abarelix was successful in achieving its primary endpoint: a demonstration of a clinically significant PSA response rate with abarelix therapy in AIPC. These studies did, however, generate important observations and produced new hypotheses. Abarelix was shown to substantially reduce serum FSH in patients who had received prior LHRH agonist therapy and in patients previously treated with an orchiectomy. The FSH suppression in the orchiectomy group, although robust on a percentage basis, was incomplete, perhaps because of chronic elevation of FSH. By several measures of efficacy, orchiectomy patients fared better than LHRH agonist patients. Considering that these same patients had higher circulating FSH concentrations, this observation is consistent with the hypothesis that targeting FSH signaling could be useful in AIPC. These studies tested a standard dose and schedule of abarelix that was not designed to maximally suppress FSH in previously treated patients, but was developed with the goal of suppressing testosterone in hormone-naïve patients. Therefore, we hypothesized that higher and/or more frequently administered doses of abarelix might more completely suppress circulating FSH in AIPC patients and that more complete FSH suppression might prove efficacious in this setting.

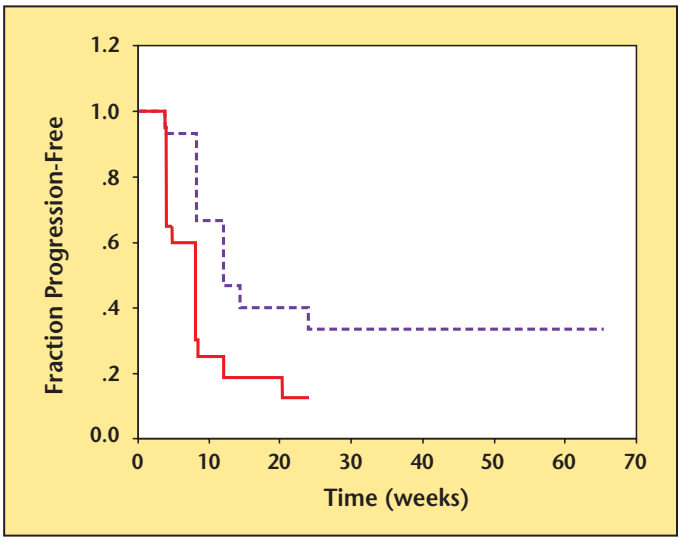

Figure 1. *Kaplan-Meier estimate of time to progression in patients treated with abarelix after failing orchiectomy (solid red line) and luteinizing hormone-releasing hormone agonist (dashed purple line) therapy.* P = .025.

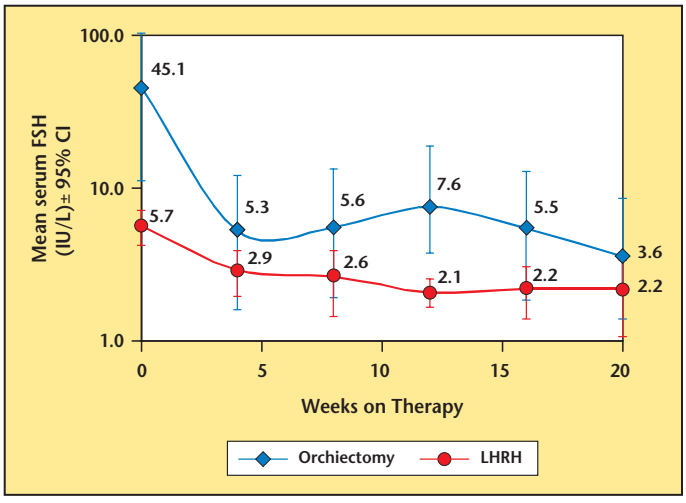

Figure 2. *Serum follicle-stimulating hormone (FSH) measured before treatment (day 0) and every 4 weeks throughout the treatment period. LHRH, luteinizing hormone-releasing hormone.*

Future Directions

In order to explore the possibility that the dosing schedule of abarelix could be optimized to better suppress FSH in patients with AIPC, a phase I trial testing more frequently dosed abarelix in AIPC patients is under way. Initially, patients in this trial will be treated with abarelix 100 mg by intramuscular injection given every 2 weeks for 12 weeks. Further studies that test the efficacy of abarelix in AIPC will be developed if dose-escalated abarelix proves safe and more effective in suppressing serum FSH in AIPC patients. ■

Acknowledgment: Supported in part by PHS grants 5 M01 RR00334-33S2 and 20000775-001 from Praecis Pharmaceuticals.

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Main Points

- Preclinical evidence supports the hypothesis that follicle-stimulating hormone (FSH) signaling contributes to progression of androgen-independent prostate cancer (AIPC).
- Patients on luteinizing hormone-releasing hormone (LHRH) agonists have modestly reduced but detectable FSH levels, whereas patients treated with orchiectomy have significantly elevated FSH levels.
- Abarelix suppresses FSH more effectively than LHRH agonists when used as front-line hormonal therapy.
- In 2 phase II studies, abarelix was tested in AIPC patients who were progressing on either LHRH agonists or after orchiectomy.
- Abarelix was shown to reduce serum FSH in AIPC patients.
- Although no responses were seen, the orchiectomy patients had considerably higher FSH levels on study entry and experienced more frequent disease stabilization.
- Ongoing studies are exploring the possibility that higher doses of abarelix may further reduce FSH in AIPC patients.
- Additional studies will be needed to determine whether further suppression of FSH would translate into clinical responses in AIPC.